Bisoprolol Therapy and The Risk of Erectile Dysfunction in Stable Coronary Artery Disease Patients

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Abstract

Background : Bisoprolol is an anti angina and ischemic therapy in patient with stable coronary artery disease (CAD). Moreover it can decrease mortality and rehospitalization rate up to 34 % and 28 %. However it is also known to increase erectile dysfunction risk. Leydig cells has beta receptor which contribute in testosterone release. The blockade of beta receptor by bisoprolol can inhibit testosterone release and cause erectile dysfunction (ED)
Method : This retrospective case control study was done by age matched paired method. Men with CAD as diagnosed by angiography were evaluated for ED. Erectile function was assessed by a 5-item version of the International Index of Erectile Function (IIEF-5). History of disease and medical record were evaluated to check history of bisoprolol therapy for the last 6 month. Depression was screened using Indonesian version of Hospital Anxiety and Depression Scale (HADS).
Result : From 157 total subject, patients were divided into 105 patients in case group and 52 patients in control group. Ninety patients (85.7%) had history of bisoprolol therapy. The odd ratio of bisoprolol to have ED risk was 2, but there was not significant statistically (95% CI 0.85-2.93; p= 0.262). From sub analysis result 5 mg bisoprolol therapy have significant statistic result to ED risk (OR 2.65, 95% CI 1.12-6.25; p=0.026). Diabetes was another confounding factor which have significant risk to ED from multivariate analysis result (OR 3.8, 95 % CI 1.65-8.88, p=0.002).
Conclussion : Stable CAD patients with bisoprolol therapy have a higher risk of ED compare with stable CAD patient without bisoprolol, however it was not statistically significant .

Keywords : Bisoprolol**;** erectile dysfunction; stable coronary artery disease

Introduction

Beta blocker are classified as one of coronary heart disease medical therapy. Beta blocker are indicated in myocardial infarction and chronic heart failure patients. Cardiac Insuficiency Bisoprolol Study II (CIBIS II) trial supported the use of betablocker in stable CAD patient.[1] Bisoprolol used may decrease mortality and rehospitalization rate upto 34% and 28 %. CIBIS II trial became evidence based for ESC guideline to include bisoprolol into one of coronary heart disease medical treatment.[2]

Bisoprolol was reported to cause erectile dysfunction as one of major complication. Bisoprolol may disrupt testosterone release from Leydig cell. Leydig cell have beta 1 receptors on its surface that have role on tertosterone secretion and metabolism. Leydig cell have approximately 25% beta 1 receptor and 75% beta-2 receptor. Disruption on testosterone release by beta blocker may cause decrease in serum testosterone level. Low serum testosterone level may impair sexual function. Bisoprolol are beta 1 selective blocker drugs which still have effect in sexual function. Therefore, side effect of bisoprolol therapy in sexual function at patient with CAD may cause erectile dysfunction.[3]

Our study aims to evaluate the risk of erectile dysfunction in patients with stable CAD treated with bisoprolol.

Methods

This study was an observational study. The study design was case control retrospective which to asses risk of erectile dysfunction in stable CAD patient.This retrospective case control study was done by age paired matched method. Subject of this research were male with stable CAD who have been evaluated for bisoprolol used for last 6 month to asses ED risk. Men with stable CAD as diagnosed by angiography were evaluated for ED. Erectile function was assessed by a 5-item version of the International Index of Erectile Function (IIEF-5). History of disease and medical record were evaluated to check history of bisoprolol therapy for the last 6 month.

The inclusion criteria for this research were patient that has been diagnosed stable CAD by angiography, active sexually for last 6 month, patient aged between 30 to 80 years, patient who had Hospital Anxiety and Depresion Scale (HADS) < 8 and agreed to parcipitate in study. The exclusion criteria were patient with history of pelvic trauma, patient has been diagnosed with stroke, parkinsonism or encephalitic

Every patient who had been diagnosed CAD by angiography was checked for history of bisoprolol used in last 6 month at Cardiology Outpatient Clinic in Dr. Sardjito General Hospital . Another medical therapy for CAD such as angiotensin receptor blocker (ARB), calcium channel blocker (CCB) and diuretic were analyzed as confounding factor.

Subject in this study were selected with age-paired match with less than 5 years in difference between age. Subjects has been taken with consecutive methods with proportion between case and control were 2:1. Patient that has been diagnosed as erectile dysfunction were included as case and patient that is not fulfill ED criteria were included as control. The

Table 1. Baseline characteristic of subjects based on the presence of erectile dysfunction

Variable	ED (n=105)	non ED (n=52)	p value
Age in year, mean± SD	55.6±7.1	52.65±7.6	0.276
BMI, mean ± SD	24.94±3.4	24.41±3.2	0.553
CAD Medical Therapy, n (%)			
Bisoprolol	90 (85.7)	39 (75)	0.262
Bisoprolol 1.25mg	10 (11.4)	9 (13.5)	0.450
Bisoprolol 2.5 mg	43 (41.9)	21(40.8)	0.400
Bisoprolol> 5 mg	37 (35.2)	9 (17.3)	0.015
Tiazide	10 (9.5)	3(5.8)	0.310
ACE Inhibitor	26 (24.9)	12 (23.1)	0.490
ARB	52 (49.5)	30 (57.7)	0.390
CCB	24 (22.9)	10 (19.2)	0.380
Traditional Risk Factor, n (%)			
Diabetes mellitus	47 (44.8)	9 (17.4)	0.001
Hypertension	61 (58.1)	26 (50)	0.390
Dyslipidemia	66 (70.2)	28 (53.8)	0.300
Smoker	63(60.0)	28 (53.8)	0.490
Coronary Artery Disease, n (%)			
CAD 1 VD	26(24.7)	18 (34.6)	0.265
CAD 2 VD	27 (25.7)	18 (34.6)	0.270
CAD 3 VD	52(49.5)	16(30.8)	0.019

ED is erectile dysfunction, SD is standard deviation, CAD is coronary artery disease, ACE is angiotensin converting enzyme, ARB is angiotensin receptor blocker, CCB is calcium channel blocker, VD is vessel disease

Table 2. Bivariate analysis of bisoprolol and ED risk

Group	ED (n=105)	no ED (n=52)	Odd ratio	95% CI	p value
Bisoprolol (+)	90	39	2	0.85-2.90	0.262

independent variable was bisoprolol used as CAD medical therapy and dependent variable of this study was ED. A statistical analysis was performed to analyse the relation between variables. An ethics committee of Faculty of Medicine Universitas Gadjah Mada – Dr. Sardjito Hospital had approved the study protocol.

Result

The number of subject in this study was 157 patients who divided into 105 patient in case group (ED) and 52 patient in control group (no ED). There was no significant difference between age in case group (55.6 ±7.071) or control group (52.65 ±7.6) with p value = 0.276. Total subjects who had bisoprolol therapy for last 6 month were 90 patients from case group and 39 patients from control group. Bisoprolol therapy in this study were divided into several dose which were 1.25 mg, 2.5mg and ≥ 5 mg. Most frequent bisoprolol used were in 2.5mg dose that is used by 43 case patient and 21 control patient. Another variable characteristic is shown in table 1

The group who had bisoprolol therapy in this study, have ED risk with odd ratio value were 2 (95% CI 0.85-2.93, p=0.262). ED risk in bisoprolol therapy were shown in table 2.

Factors in CAD patient who had ED as risk was shown in table 3 below. There were 2 variables that had significant risk for ED in CAD patient. Those variable were diabetes (OR 3.87 95% CI 1.7- 8.74) and CAD 3 VD (OR 2.2 95% CI 1.09-4.45). Another odd ratio value for each variable was shown in table 3

From multivariate analysis for risk factor of ED we have 2 significant variables. Those were bisoprolol therapy > 5 mg (OR 2.65, 95% CI 1.12 -6.26) and diabetes (OR 3.8 95% CI 1.65- 888) whose significantly increase risk of ED. Complete multivariate analysis result wasshown in table 4.

Table 3. Variables as risk factor of ED

Variables	Odd ratio	95% CI	p value
Medical therapy			
Bisoprolol	2	0.85 – 2.93	0.260
Bisoprolol 5 mg	2.32	1.07 – 5.51	0.037*
Thiazide	1.72	0.45 – 6.53	0.319
CCB	1.24	0.54 – 2.80	0.380
ACE	1.09	0.50 - 2.40	0.490
ARB	0.71	0.37 – 1.41	0.390
Traditional risk factor			
Diabetes mellitus	3.87	1.70 – 8.74	0.001*
Dyslipidemia	1.45	0.55 – 11.90	0.303
Hypertension	1.38	0.71 – 2.70	0.395
Smoking	1.28	0.65 – 2.51	0.495
Coronary artery disease			
1VD, n(%)	0.84	0.66 – 1.11	0.260
2VD, n(%)	0.86	0.69 – 1.17	0.270
3VD, n(%)	2.20	1.09 – 4.45	0.041*

ACE is angiotensin converting enzyme, ARB is angiotensin receptor blocker, CCB is calcium channel blocker, VD is vessel disease, CI is confidence interval

Table 4. Multivariate analysis for ED risk in CAD patients

Variable	Odd ratio	95% CI	P value
Bisoprolol ≥ 5 mg	2.65	1.12– 6.26	0.026
Diabetes	3.80	1.65 – 8.88	0.002
CAD 3VD	2.01	0.96 – 4.20	0.063

CAD is coronary artery disease, VD is vessel disease, CI is confidence interval

Discussion

A randomized controlled trial has been done to evaluate bisoprolol therapy response as an anti hypertension therapy. Erectile dysfunction (ED) has been analyzed as secondary outcome of bisoprolol therapy as an antihypertension.

Cross sectional study about ED prevalence in hypertensive patient on beta blokertherapy has been reported. About 31-35% hypertensive patient with beta bloker therapy have sexual dysfunction as a secondary outcome. There was significant IIEF score difference between patient with bisoprolol and nebivolol therapy (21 vs 25; p<0.01).[4]

A cohort study, which evaluated hypertensive therapy to erectile dysfunction risk, has been conducted in 2006. Two thousand five hundreds and ten hypertensive patients received medical therapy such as calcium channel blocker (CCB) (RR 1,6; 95% CI 1-2,4), diuretic (RR 1,3; 95 % CI 0,7-2,4) and Angiotensin ConvertingEnzyme inhibitor/ACE I (RR 0,9; 95 % CI 0,6-1,9). Beta blocker have highest relative risk (RR 1.97, 95% CI 0.9-3.2). These study shows that B blocker therapy may decrease sexual function in hypertensive patient.[5]

Bisoprolol is B1 selective drugs, which can suppres Leydig cell activity to synthesis testosterone hormone. Furthermone, bisoprolol will decrease total testosterone serum level. Disturbance in total testosterone serum level will increase risk of ED.[7] The risk of ED in CAD patient has been assesed by IIEF score. Bisoprolol therapy in all dose did not give significant risk to ED in CAD patient (OR: 2.95 % CI 0.85-3.1; p= 0.26). However, in sub analysis there was significant ED risk for bisoprolol therapy ≥ 5 mg (OR 2.65, 95% CI 1.12 – 6.26).

Leydig cell has 25% B1 receptor on its surface which has function to stimulate testosterone release. B1 selective drugs will bind in these receptor and inhibit testosterone release. Decrease in total testosterone secretion will increase risk of ED. This study havesimilar result based on previous hypothesis about testosterone binding disturbance in leydig cell.[3]

In 2002, Fogari *et al* found atenolol (another b1 selective drugs) was also decrease testosterone secretion that cause ED. Fogari found that atenolol therapy which given for 6 month will increase ED risk in hypertensive patient. This study proves that atenolol as B1 selective drugs (similar with bisoprolol) also increase ED risk based on same pathophysiology.[8]

Diabetes mellitus was one of confounding factor that significantly increase ED risk in this study with OR value was 3.8 (P = 002). Martin et al. also found in 2001 that diabetes was one of traditional risk factor that have significantly increase ED risk. Another confounding factor (CAD 3 VD, ARB, CCB, diuretic and smoking) did not have significant result to increase ED risk in this study.

Study limitation

In this study, testosterone serum level, which can affect risk of ED,was not measured. ED risk was measuredby IIEF quesioner. This study used case controlled age paired match method when randomized control trial will give better result but that method has ethical issue. Diabetes, which was most significant confounding factor of this study was not, excluded so there still bias possibility for result of this study.

Conclusion

Coronary artery disease patients who had bisoprolol therapy for last 6 months have increase risk of erectile dysfunction but it was not statistically significant. Significant result was only found in patient who had bisoprolol therapy ≥ 5 mg in dose.

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